REMARKS

Specification Amendments

The Office Action states that the specification is objected to because "Eraser" [0117] should be "Fraser". However, the specification filed with the USPTO on February 4, 2005 recites "Fraser", not "Eraser". Therefore, Applicants believe no amendment is necessary.

The specification is objected to for referencing Bourne et al, 1990 and Marshall et al, 1991 [0010, 0117] when referring to p21. According to the Office Action, the protein of Bourne et al and Marshall et al is the p21 ras GTPase, rather than p21CDKN1/WAF1/CIP1, discussed in the instant application. The appropriate paragraphs of the specification have been amended to delete reference to Bourne et al, 1990 and Marshall et al.

The specification is objected to for referencing Hay et al 1994 when referring to the GMR-p21 transgene [0117]. According to the Office Action, Hay et al fails to comprise the term p21, GMR-p21, or GMR-p21 transgene. The appropriate paragraph of the specification has been amended to delete reference to Bourne et al, 1990 and Marshall et al.

Claim Amendments

Claims 1, 3, 4, 5, 7-11, 13, 15, 16, 20, 22-25, and 26-30 are pending in this application. Claim 6 was previously cancelled without prejudice or disclaimer. Claims 4, 5, 7-11, 13, 15, 20, and 22-25 were previously withdrawn without prejudice, as being drawn to non-elected subject matter. Claims 26 and 30 have been cancelled without prejudice with this amendment. Claims 1, 3, and 16 have been amended.

Claims 1 and 16 have been amended to recite providing an assay system comprising mammalian cultured cells comprising a CSNK1G nucleic acid comprising any of SEQ ID NOs: 1-12 or polypeptide encoded thereby. Support for the amendment can be found at, for example, page 4. Claim 3 has been amended to recite that the cell in

culture is a mammalian cell. Support for the amendment can be found at, for example, at page 34.

The claim amendments are made solely in an effort to advance prosecution and are made without prejudice or disclaimer, without intent to acquiesce in any rejection of record, and without intent to abandon any previously claimed subject matter. Additionally, these amendments and cancellation are not and should not be construed as admissions regarding the patentability of the claimed or canceled subject matter. Applicants reserve the right to pursue the subject matter of previously presented claims in this or in any other appropriate patent application. No new matter has been added by way of these amendments. Accordingly, Applicants respectfully request the entry of the amendments presented.

The 35 USC § 101 Rejection

Claims 1, 3, and 26-30 were rejected under 35 USC § 101 because the claimed invention allegedly lacks patentable utility. Specifically, the Office alleged that the claims lack a specific and substantial utility. Applicants submit that claims 26 and 30 have been canceled, rendering the rejection moot as to those claims. With respect to the pending claims, Applicants respectfully traverse the rejections.

The Office alleged that the presently claimed methods lack utility because the method "is designed to merely identify a 'candidate' p21 pathway modulator. Thus, the method fails to have a specific and substantial benefit to the public without further research to determine if the 'candidate' modulator is, in fact, a modulator of the p21 pathway. Practicing the recited steps has no immediate benefit to the public."

An invention has specific utility if the identified use is well-defined and has a particular benefit to the public and is specific to the subject matter claimed. As explained in the specification, p21 is involved in the regulation of cell growth. Specifically, p21 is a cell cycle control protein that inhibits cyclin-kinase activity and mediates p53 suppression of tumor cell growth. (specification, page 1). Applicants have discovered that casein kinase I (CSNK1G), a serine/threonine kinase, modifies the p21 pathway. (specification, at pages 2-3). As explained in the specification, CSNK1G proteins and nucleic acids can be used to identify p21 modulating agents. The identification of such agents can be used in the study and treatment of disorders associated with defective or

impaired p21 function, such as cancer . (specification, at pages 2-4). Thus, the invention provides screening assays that have specific utility for identifying p21 pathway modulating agents, which agents are candidates for the further development of diagnostic and therapeutic modalities for the diagnosis and treatment of disorders associated with defective p21. The specification describes additional uses at pages 32-34.

A claimed invention has substantial utility if it defines a "real world" or "practical" use. According to the MPEP, "any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient, at least with regard to defining a 'substantial' utility". MPEP §2107.01 I. The claimed methods have a practical use for identifying p21 pathway modulating agents, which agents are therapeutic candidates for the diagnosis and treatment of disorders associated with defective p21.

The Office asserted that the present claims fail to have a specific and substantial benefit to the public without further research to determine if the 'candidate' modulator is, in fact, a modulator of the a p21 pathway. The Office concluded that the recited steps have no immediate benefit to the public. However, contrary to the Office's assertion, the claimed invention does indeed have an immediate benefit to the public. Applicants have discovered that CSNK1G modulates the p21 pathway. Thus, among other things, the claimed screening assays employing CSNK1G polypeptides or nucleic acids have the immediate benefit of identifying those compounds that modulate p21. The fact that the identified compounds may require additional testing to confirm p21 pathway modulation does not detract from the invention's immediate benefit of identifying specific compounds (out of potentially hundreds of compounds) that modulate p21. Furthermore, the fact that further research may be indicated does not preclude a finding of substantial utility. In this regard, the Federal Circuit has specifically determined that the term "benefit to the public" is not interpreted "to mean that products or services based on the claimed invention must be 'currently available' to the public in order to satisfy the utility requirement." MPEP §2107.01, citing *Brenner v. Manson*, 383 U.S. 519, 534-35 (1966).

Finally, Applicants point out that the Patent Office itself has recognized the utility of identifying "candidate" test agents. Several patents have issued with claims similar to the instant application. See, for example, US Patent Nos. 7,507,547; 7,501,395; 7,504,227; 7,498,134; and 7,498,127.

The Office further argued that a method of assaying for or identifying a material that itself has no specific and/or substantial utility does not satisfy 35 USC 101. However, for the reasons provided herein, Applicants submit that the presently claimed methods are used to assay for a p21 modulator, which modulator has specific and substantial utility.

For the reasons discussed above, the pending claims have specific and substantial utility. Accordingly, the Applicants respectfully request withdrawal of the 35 U.S.C. §101 rejections.

The 35 USC § 112, Second Paragraph, Rejections

Claims 1, 3, 16 and 26-30 were rejected under 35 USC § 112, second paragraph, as allegedly being indefinite. Applicants respectfully traverse the rejections.

Specifically, the Office stated that the phrase "full-length wildtype CSNK1G polypeptides and nucleic acids" renders the claims indefinite. Without acceding to the merits of the rejection, and solely in an effort to advance prosecution, claims 1 and 16 have been amended to remove the phrase "full-length wildtype CSNK1G polypeptides and nucleic acids" and to recite instead "a CSNK1G nucleic acid comprising any of SEQ ID NOs: 1-12 or polypeptide encoded thereby". Applicants submit the claims, as amended, are definite and respectfully request withdrawal of the rejections.

In addition, the Office stated that the term "wildtype" recited in claims 1 and 16 renders the claims indefinite. Without acceding to the merits of the rejection, and solely in an effort to advance prosecution, claims 1 and 16 have been amended to remove the term "wildtype", thereby rendering the rejection moot. Applicants submit the claims, as amended, are definite and respectfully request withdrawal of the rejections.

The Office also stated that the phrase "phenotypic change" renders the claims indefinite because the specification fails to define the metes and bounds of "phenotypic change". Applicants submit that one skilled in the art would know that the term "phenotypic change" in mammalian cells refers to changes in cell appearance (ie morphology, size, etc) and cell behavior (ie function), for example, changes in cell apoptosis, proliferation, progression through cell-cycle, angiogenesis, adhesion, tubulogenesis, migration, sprouting, etc, as described throughout the specification.

The Office further stated that claim 3 is indefinite because it allegedly lacks proper antecedent basis. Claim 3 has been amended to recite a "mammalian" cultured cells, thereby rendering the rejection moot. Applicants respectfully request withdrawal of the rejection.

The Office further stated that claim 16 is indefinite because it allegedly lacks proper antecedent basis. Claim 16 has been amended to recite a "the phenotype change", thereby rendering the rejection moot. Applicants respectfully request withdrawal of the rejection.

For the reasons discussed above, the pending claims are clear and definite. Accordingly, the Applicants respectfully request withdrawal of the 35 U.S.C. §112, second paragraph rejections.

The 35 USC § 112, First Paragraph, Rejections

Enablement

Claims 1, 3, 16, and 26-20 were rejected under 35 USC § 112, first paragraph, as allegedly not being enabled. Applicants submit that claims 26 and 30 have been canceled, rendering the rejection moot as to those claims. With respect to the pending claims, Applicants respectfully traverse the rejections.

Applicants submit that the instant claims satisfy the enablement requirement for all of the reasons set forth in the previous response filed on January 14, 2008, which is incorporated herewith.

Despite Applicants arguments, the Office maintained that the claims are not enabled because the specification allegedly fails to teach a method for identifying a candidate p21 pathway modulator by assessing the proliferation of a mammalian cultured cell expressing the genus of any "full-length wildtype CSNK1G polypeptides and nucleic acids".

The claims have been amended to recite a method for identifying a candidate p21 pathway modulator employing a mammalian cell that expresses a CSNK1G nucleic acid comprising any of SEQ ID NOs: 1-12 or polypeptide encoded thereby. In this regard, the

specification clearly describes and provides the sequences of SEQ ID NOs: 1-12. Furthermore, one skilled in the art would be able to determine the structure/sequences of a polypeptide encoded by any of SEQ ID NOs: 1-12. Thus, the claims are enabled across the genus of claimed CSNK1G nucleic acids and polypeptides.

The Office asserted that the claims are not enabled because the specification does not provide any evidence that CSNK1G acts via the p21 pathway. The Office acknowledged that the specification teaches a genetic screen wherein one set of flies over-expressing p21 (having the mutant phenotype of "reduced, rough eyes") is crossed with flies having random genetic mutations via transposon-mediated mutation, which screen resulted in identifying the GISH (Drosophila CSNK1G) gene as an "enhancer of the eye phenotype". However, the Office asserted that a skilled artisan would not have concluded that, more likely than not, CSNK1G acts via the p21 pathway for the following reasons: (1) it is unclear what the specification means by "enhancer of the eye phenotype"; (2) the specification provides no evidence that p21 and CSNK1G act via the same signal transduction pathways in the development of "rough eye"; and (3) the art teaches that "rough eye" in Drosophila is a gross phenotype that is affected by many signaling pathways (referring to the teachings of Kumar et al, 1997 and Wolff et al, 1991). Thus, the Office concluded that without further experimentation at the molecular level, the skilled artisan cannot deduce that, more likely than not, any effects of p21 and CSNK1G on "rough eye" are mediated by the same signal transduction pathway.

Applicants submit that, contrary to the Office's assertions, one skilled in the art would readily recognize that the effects of p21 and CSNK1G on "rough eye" are mediated by the same signal transduction pathway. First, Applicants submit generally that genetic screens, such as the p21 genetic screen performed by the Applicants and described in the specification, are well-established and accepted methods for geneticists to identify genes involved in specific cellular pathways of interest. Second, with specific respect to the p21 pathway screen described in the specification, Applicants submit that the "rough eye" phenotype observed in the drosophila eye caused by the GMR-p21 transgene (ie, the transgene used in Applicants' genetic screen, see specification at p. 34) is a well-characterized and accepted animal model for specifically measuring the effect on the p21 pathway (see de Nooij, Science, 270: 983-985). The GMR-p21 transgene results in the over-expression of p21, which causes cell-cycle arrest and a decrease in cell proliferation in the eye. In fact, as described in detail in the de Nooij et al. reference, the effects of GMR-p21 transgene expression on cell-cycle regulation and cell proliferation

in the drosophila eye are known at the molecular level. For example, it is known that the GMR-p21 transgene targets expression of the p21 gene to cells posterior to the morphogeniuc furrow in the eye imaginal disc, which abolishes the second mitotic wave during eye development. Thus, expression of the GMR-transgene is able to prevent G1-arrested cells posterior to the furrow from entering S phase. This disrupts the eye structure, resulting the "rough eye" phenotype. Others have relied on the GMR-p21 transgene model in drosophila to identify genes specifically involved in the p21 pathway. See, for example, Stachling-Hampton et al., Genetics, 153: 275-287 (1999), which showed that poc alleles suppress the GMR-p21 rough eye phenotype.

To address the Office's specific arguments, Applicants submit that one skilled in the art (ie, a geneticist) would understand what is meant by "enhancer of the eye phenotype", as the "enhancer" and "suppressor terminology is routinely used by geneticists in describing the phenotypic results of genetic screens. Thus, one skilled in the art would understand the following: the genetic screen performed by the Applicants crossed female drosophila expressing the GMR-p21 transgene (resulting in over-expression of p21, cell-cycle arrest (decrease in cell proliferation), and the rough eye phenotype) with male drosophila having a mutated genome via the insertion of transposons. Resulting progeny carrying both the transgene and the transposons were scored for the effect on rough eye phenotype, ie whether the rough eye phenotype was enhanced (more pronounced) or suppressed (less pronounced, ie more like wildtype eyes). Mutated GISH was identified as an enhancer of the rough eye phenotype, indicating that GISH loss of function results in more pronounced rough eye phenotype, due to greater cell cycle arrest and decreased cell proliferation in the eye. In other words, modulators that cause a decrease in GISH expression or activity (GISH loss of function) result in the enhanced rough eye phenotype due to increased cell-cycle arrest and decreased cell proliferation in the eye. The human ortholog of GISH, CSNKIG, functions in the same manner, which is confirmed by the RNAi experiments. Modulators (siRNA) causing a decrease in CSNG1K expression result in a decrease in cell proliferation in several exemplary mammalian cells.

Further, for the reasons discussed above and further explained in the cited de Nooij et al and Stachling-Hampton et al. references, Applicants submit that the results of the described drosphila screen provides direct evidence that p21 and GISH act via the same signal transduction pathways in the development of "rough eye" and that the art teaches that GMR-p21 induced "rough eye" in Drosophila is a specific model for the p21 pathway

and not a gross phenotype that is affected by many signaling pathways. The Office refers to the teachings of Kumar et al, 1997 and Wolff et al, 1991 to support its argument that the "rough eye" phenotype is not a specific indicator for the p21 pathway, however, Applicants submit that Kumar et al and Wolff et al do not describe the GMR-p21 induced "rough eye" model. For the reasons stated, Applicants submit that one skilled in the art would recognize that the GMR-p21 induced "rough eye" model is specific for determining gene involved in the p21 pathway.

Further, while the Office acknowledged that Drosophila is a useful model for some mammalian pathways and disorders, it asserted that not all mammalian pathways and disorders can be modeled in Drosophila, alleging that Ollmann et al, 2000 teaches that Drosophila is not a useful model for the role of the mammalian p53/p21 pathway in inducing cell cycle arrest at G1. Applicants again submit that Ollmann does not describe or relate to the GMR-p21 genetic screen, which is recognized by skilled artisans as a useful model for specifically identifying genes involved in the p21 pathway.

The Office also asserted that the Chintapalli et al reference cannot be used as evidence for enablement because it was published after this Application's priority date. While Applicants disagree, submitted herewith are references which discusses the usefulness of drosophila as a model for studying human gene function. Rubin et al. indicate that of 289 human genes, 177 appear to have an ortholog in drosophila, and of the cancer genes surveyed, 68% appear to have drosophila orthologs, including the p53 gene. See Rubin et al., Science 287, 2204-2215 (2000). The Scangos reference (Nature Biotechnology, 15: 1220-1221 (1997)) teaches that most human genes have counterparts in drosophila and that the pathways characterized in humans and in drosophila demonstrate that, in a majority of cases, entire biochemical pathways have been conserved.

The Office also argued that searches of the STN, EAST, and NCBI/Entrez databases failed to teach Drosophila as a model for a mammalian CSNK1G/p21 pathway or any disorder due to alteration of a CSNK1G/p21 pathway in mammals (search results of record). However, Applicants submit that the lack of teaching is a reflection of the novelty of the presently claimed methods.

The Office further argued that while the p21 pathway is involved in the regulation of cell growth and proliferation in some systems and the specification teaches that SEQ ID NO: 1, 8, and 11 are elevated in some tumor cells and that RNAi of SEQ ID NO: 1, 8,

and 11 decrease proliferation in LX1, 231T, A549 cell lines, the specification fails to provide a link between any CSNK1G mediated proliferation and any p21-mediated proliferation in any mammalian cell system. Applicants submit that, for the reasons discussed herein, the genetic screen establishes the link between the p21 pathway and GISH/CSNK1G. The RNAi data in mammalian cells further confirms the link between the p21 pathway and CSNK1G in mammalian cells and demonstrates the usefulness of the claimed screening assay to identify p21 candidate modulators.

Written Description

Claims 1, 3, 16, and 26-30 were rejected under 35 USC § 112, first paragraph, as allegedly lacking written description. Applicants respectfully traverse the rejections.

Applicants submit that the instant claims satisfy the written description requirement for all of the reasons set forth in the previous response filed on January 14, 2008, which is incorporated herewith.

Despite Applicants arguments, the Office maintained that the claims do not satisfy the written description requirement because the specification allegedly fails to sufficiently describe the recited invention which encompasses any method for identifying a candidate p21 pathway modulator by assessing the proliferation of any cultured mammalian cell expressing CSNK1G. Thus, the Office concluded that the method was not described in the specification in such a way that a skilled artisan would recognize that Applicants were in possession at the time of filing. (specification at page 12).

The claims have been amended to recite a method for identifying a candidate p21 pathway modulator employing a mammalian cell comprising a CSNK1G nucleic acid comprising any of SEQ ID NOs: 1-12 or polypeptide encoded thereby in a cell proliferation assay system and a test agent that modulates the expression of CSNK1G.

Contrary to the Office's allegation, the specification sufficiently describes a number of exemplary cultured mammalian cells that can be used in the claimed methods, including for example, HCT116 colon cancer cells, LX1 small lung cancer cells, 231T breast cancer cells, and A549 lung cancer cells. Further, as the Office clearly recognized, it was known in the art that CSNK1G is ubiquitously expressed in mammalian cells (see Kusuda et al. 2000). In addition, the specification sufficiently describes a number of

cellular assays that can be used in the claimed screening methods, including, for example, cell proliferation, cell-cycle, cell adhesion, cell sprouting, angiogenesis, tubulogenesis, cell migration, cell apoptosis, and other assays (specification at pages 20-19).

Despite the written description support, the Office asserted that the specification fails to provide any evidence that any mammalian cells can be used in the claimed methods. Specifically, the Office stated that "[n]o example is provided for a method, using an inhibitor of CSNK1G expression, for identifying a p21 pathway modulator using a mammalian cell. ... Applicants merely rely on the results from Drosophila and assert that the recited method can be performed in mammalian cells; leaving to the public the task of determining if said assertion is correct."

First, Applicants submit that the written description requirement does not require an actual reduction to practice. M.P.E.P. § 2163. Accordingly, an Applicant need not show that the invention will work for its intended purpose to satisfy the written description requirement. Further, although an example is not required to satisfy the written description requirement, contrary to the Office's assertion, the specification does indeed provide several examples of methods for identifying a p21 pathway modulator in a mammalian cell using an inhibitor of CSNK1G expression. The specification provides examples of identifying various p21 pathway modulators (siRNA against CSNK1G comprising SEQ ID NO: 1, siRNA against CSNK1G comprising SEQ ID NO: 8, and siRNA against CSNK1G comprising SEQ ID NO: 11) in various mammalian cells (LXI small cell lung cancer cells, 231T breast cancer cells, and A549 cells) using various cell proliferation assays (BrdU, Cell Titer-Glo, and MTS cell proliferation assays). See specification on page 39. Although the examples on page 39 were not described individually in the specification, they represent a total of 21 different examples of methods for identifying a p21 pathway modulator in a mammalian cell (three different modulators, each tested using two different cell proliferation assays in two different cell types and a third cell proliferation assay in a third cell type). The specification provides further examples of methods for identifying a p21 pathway modulator in a mammalian cell using various p21 pathway modulators (siRNA against CSNK1G comprising SEQ ID NO: 1 and siRNA against CSNK1G comprising SEQ ID NO: 11) in LXI small cell lung cancer cells using a nucleosome ELISA apoptosis assay.

The Office rejected claim 26 as failing to comply with the written description requirement because the specification allegedly does not describe contacting a mammalian cell with an anti-CSNK1G antibody that modulates the activity of CSNK1G

inside the mammalian cell. Without acceding to the merits of the rejection, claim 26 has been cancelled without prejudice, rendering the rejection moot.

The Office rejected claim 30 as failing to comply with the written description requirement, arguing that the specification fails to describe any successful species of a genus of methods using an agent that modulates CSNK1G activity to restore the function of p21 in mammalian p21 knock-out cells. Without acceding to the merits of the rejection, claim 30 has been cancelled without prejudice, rendering the rejection moot.

For the reasons discussed above, the pending claims satisfy the written description requirement. Accordingly, the Applicants respectfully request withdrawal of the 35 U.S.C. §112, first paragraph, rejections based on lack of written description.

CONCLUSION

In view of the above remarks, the application is considered to be in good and proper form for allowance and the Examiner is respectfully requested to pass this application to issue.

Respectfully submitted,
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